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(71) Applicant *(for all designated States except US):* RHONE-POULENC RORER INTERNATIONAL (HOLDINGS) INC. [US/US]; 40 Cape Henlopen Drive, Lewes, DE 19958 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* SPADA, Alfred, P. [US/US]; 473 Painter Way, Lansdale, PA 19446 (US). MAGUIRE, Martin, P. [US/US]; 649 S. Henderson Road, A-512, King of Prussia, PA 19406 (US). PERSONS, Paul, E. [US/US]; 649 S. Henderson Road, A-507, King of Prussia, PA 19406 (US). MYERS, Michael, R. [US/US]; 205 Lincoln Road, Reading, PA 19606 (US).

(74) Agents: NICHOLSON, James, A. et al.; Rhone-Poulenc Rorer Inc., 500 Arcola Road, P.O. Box 1200, Collegeville, PA 19426 (US).

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(54) Title: BIS MONO-AND BICYCLIC ARYL AND HETEROARYL COMPOUNDS WHICH INHIBIT EGF AND/OR PDGF RECEPTOR TYROSINE KINASE

(57) Abstract

This invention relates to bis mono- and/or bicyclic aryl and/or heteroaryl compounds exhibiting protein tyrosine kinase inhibition activity. More specifically, it relates to the method of inhibiting abnormal cell proliferation in a patient suffering from a disorder characterized by such proliferation comprising the administration thereto of an EGF and/or PDGF receptor inhibiting effective amount of said bis mono- and/or bicyclic aryl and/or heteroaryl compound and to the preparation of said compounds and their use in pharmaceutical compositions used in this method.

BIS MONO- AND BICYCLIC ARYL AND HETEROARYL COMPOUNDS WHICH INHIBIT EGF AND/OR PDGF RECEPTOR TYROSINE KINASE

Field of the Invention

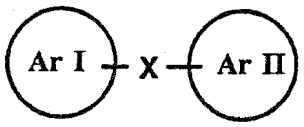
This invention relates to the inhibition of cell proliferation. More specifically, this invention relates to the use of bis mono- and/or bicyclic aryl and/or heteroaryl compounds in inhibiting cell proliferation, including compounds which are useful protein tyrosine kinase (PTK) inhibitors.

Normal cellular reproduction is believed to be triggered by the exposure of the cellular substrate to one or more growth factors, examples of which are insulin, epidermal growth factor (EGF) and platelet-derived growth factor (PDGF). Such growth factor receptors are imbedded in and penetrate through the cellular membrane. The initiation of cellular reproduction is believed to occur when a growth factor binds to the corresponding receptor on the external surface of the cellular membrane. This growth factor-receptor binding alters the chemical characteristics of that portion of the receptor which exists within the cell and which functions as an enzyme to catalyze phosphorylation of either an intracellular substrate or the receptor itself, the latter being referred to as autophosphorylation. Examples of such phosphorylation enzymes include tyrosine kinases, which catalyze phosphorylation of tyrosine amino acid residues of substrate proteins.

Many disease states are characterized by the uncontrolled reproduction of cells. These disease states involve a variety of cell types and include disorders such as leukemia, cancer, psoriasis, inflammatory diseases, bone diseases, atherosclerosis and restenosis occuring subsequent to angioplastic procedures. The inhibition of tyrosine kinase is believed to have utility in the control of uncontrolled cellular reproduction, i.e., cellular proliferative disorders.

Another aspect of the present invention relates to pharmaceutical compositions comprising, in admixture with a pharmaceutically acceptable carrier, a pharmaceutically effective amount of a novel compound of the aforementioned type. Another aspect of this invention comprises novel compounds useful in the practice of the present method.

With respect to the method aspects of this invention, the compounds described by Formula I below constitute a class of the aforementioned bis mono- and/or bicyclic aryl, heteroaryl, carbocyclic or heterocarbocyclic compounds for use in the practice of the present invention:



Formula I

where:

Ar I and **Ar II** are independently a substituted or unsubstituted mono- or bicyclic ring, said rings optionally substituted with 0 to about 3 R groups; and

X is $(CHR_1)_{0-4}$ or $(CHR_1)_m$-Z-$(CHR_1)_n$ where Z is O, NR', S, SO or SO_2, m and n are 0-3 and m+n=0-3 and R_1 and R' are independently hydrogen or alkyl; or a pharmaceutically acceptable salt thereof.

Preferably, **Ar I** is a substituted or unsubstituted mono- or bicyclic aryl or heteroaryl ring system of about 5 to about 12 atoms and where each monocyclic ring may contain 0 to about 3 hetero atoms, and each bicyclic ring may contain 0 to about 4 hetero atoms selected from N, O and S provided said hetero atoms are not vicinal oxygen and/or sulfur atoms and where the substituents may be located at any appropriate position of the ring system and are described by R.;

Ar II may be as described for **Ar I** or it may also be saturated carbocyclic wherein said ring comprises either a substituted or unsubstituted monocyclic ring containing 0 to about 2 hetero atoms, or a bicyclic ring containing 0 to about 4 hetero atoms; or a pharmaceutically acceptable salt thereof.

As employed above and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Monocyclic aryl" means a carbocyclic and/or heterocyclic aromatic ring. Preferred rings include phenyl, thienyl, pyridyl, 2(1H)-pyridonyl, 4(1H)-pyridonyl, furyl, pyrimidinyl, imidazolyl, thiazolyl, oxazolyl and tetrazolyl.

"Bicyclic aryl" means a bicyclic ring system composed of two fused carbocyclic and/or heterocyclic aromatic rings. Preferred rings include naphthyl, indolyl, benzothienyl, benzofuranyl, quinolinyl, chromonyl, 1(2H)-isoquinolonyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, quinoxalinyl, naphthyridinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"Alkyl", either alone or with various substituents defined herein, means a saturated aliphatic hydrocarbon, either branched- or straight-chained. Preferred alkyl is "loweralkyl" having about 1 to about 6 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, butyl, sec-butyl, t-butyl, amyl and hexyl.

"Alkoxy" refers to an alkyl-O-group. Preferred alkoxy groups include methoxy, ethoxy, propoxy and butoxy.

"Aryloxy" refers to an aryl-O-group. The preferred aryloxy group is phenoxy.

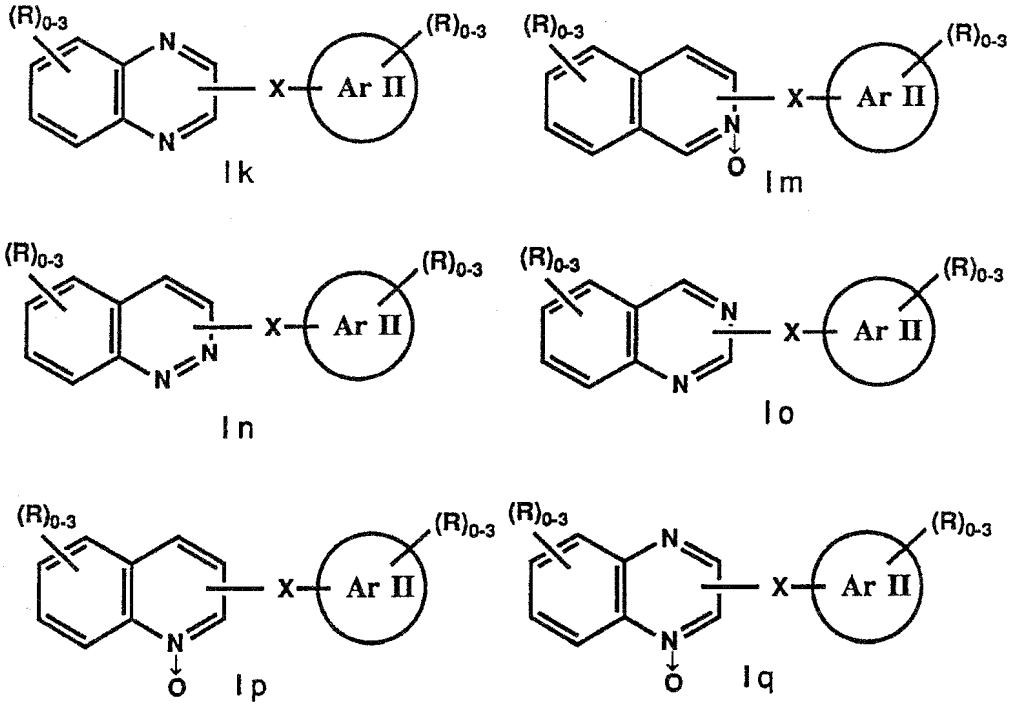
"Aralkyl" means an alkyl group substituted by an aryl radical. The preferred aralkyl groups are benzyl or phenethyl.

The preferred aralkoxy groups are benzyloxy and phenethoxy.

The preferred acyloxy group is acetoxy and benzyloxy;

"Halo" means a halogen. Preferred halogens include chloride, bromide and fluoride.

The preferred haloalkyl group is trifluoromethyl.

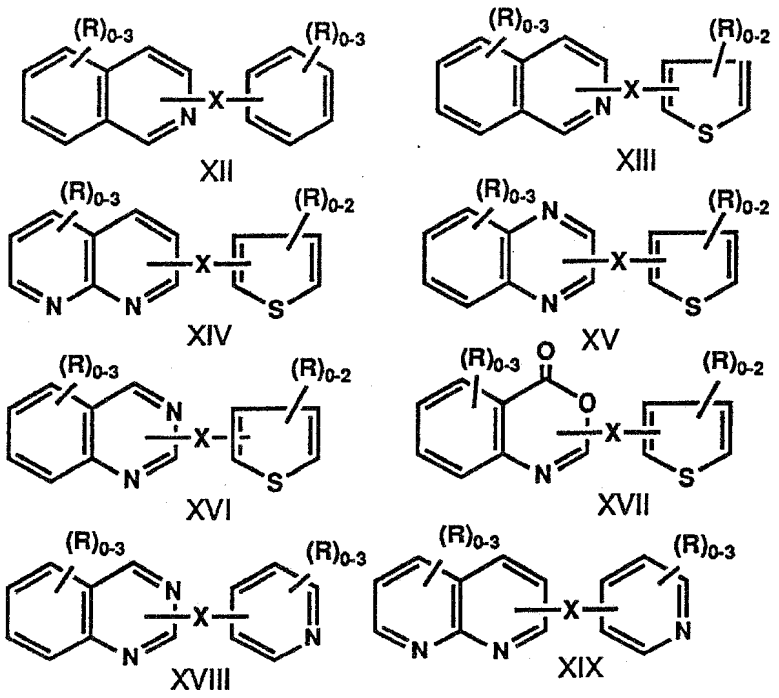


Of course it is to be understood that the R groups which are substituted in the above formulae I a- I q are located at any suitable and compatable position of the monocyclic ring or each of the rings of the bicyclic system.

A special embodiment of this invention includes those compounds of the above formulae I a- I q where **Ar II** is thienyl, phenyl, pyridyl, quinolinyl, indolyl, furanyl, imidazolyl, 2(1H)-pyridonyl, 1(2H)-isoquinolonyl and thiazolyl.

A further special embodiment of this invention includes those compounds of formulae I a- I q where **Ar II** is phenyl or thienyl.

Compounds within the scope of this invention inhibit the growth factor induced autophosphorylation of PDGF and/or EGF receptors. It is believed that therapeutically useful PTK inhibiting compounds should not have appreciable activity as inhibitors of serine or threonine kinase systems. In addition these compounds should inhibit growth factor-induced cell proliferation. Compounds meeting these criteria are of considerable value and are particularly useful in the practice of the present invention. Compounds exhibiting selectivity for either of the above receptors are described herein. Certain of these are described by Formulae II-XIX where:



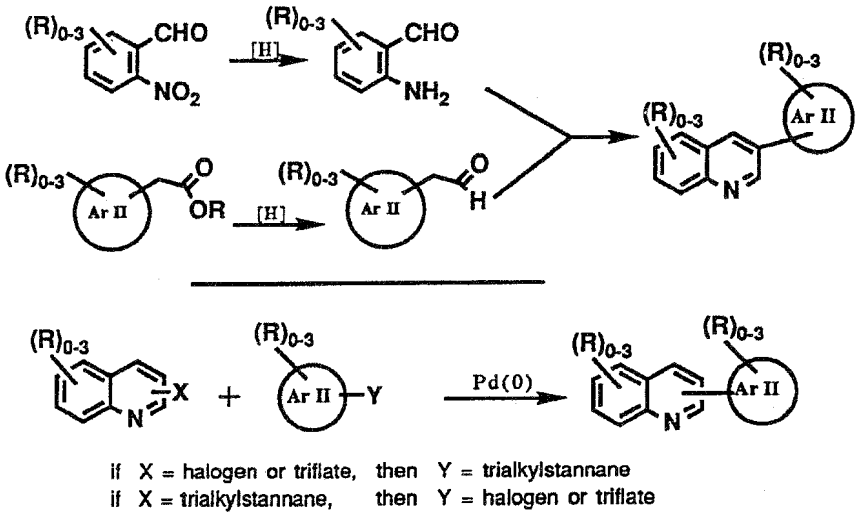
where R is independently hydrogen, loweralkyl, loweralkoxy, hydroxy, halo or trifluoromethyl.

The most preferred compounds are described where the rings are substituted independently by hydrogen, hydroxy, methoxy, ethoxy, chloro, bromo, fluoro or trifluoromethyl.

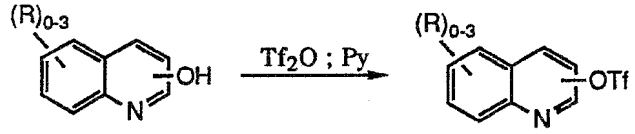
The compounds of this invention may be useful in the form of the free base, in the form of salts and as a hydrate. All forms are within the scope of the invention. Acid addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compound are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt per se is desired only as an intermediate product as, for example, when the salt is formed only for

where X is halogen or triflate and Y is trialkylstannane and R and n are as previously described.

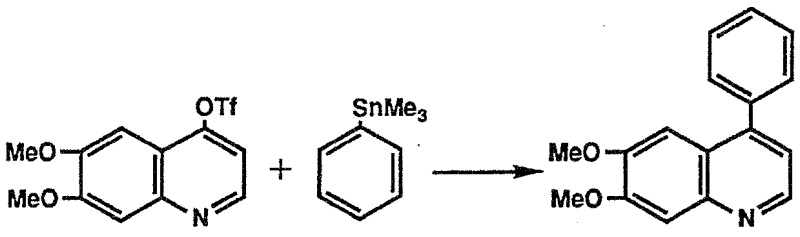
Preparation of aryl or heteroaryl substituted quinolines may be prepared as follows.



The triflate may be prepared from the corresponding alcohol with triflic anhydride (trifluoromethanesulfonic anhydride) in pyridine



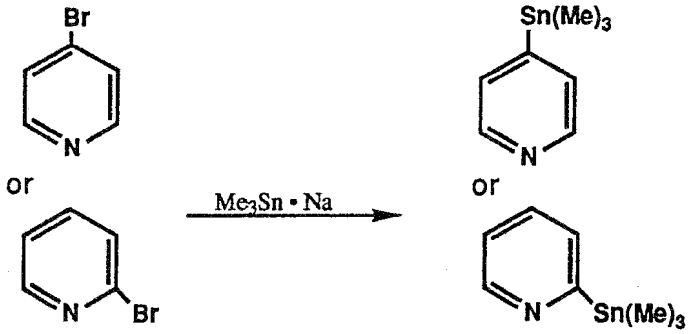
Other triflates suitable for coupling with the aryl and heteroarylstannanes may be prepared in a similar manner.



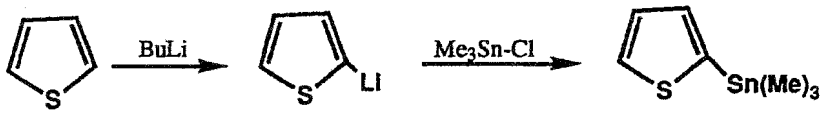
The aryl and heteroarylstannanes may be prepared from the corresponding halide (preferably bromide or iodide) by conversion to the aryllithium (by reaction with t-butyllithium at decreased temperatures, preferably about -78° C) followed by reaction with a halotrialkylstannane. The following reaction schemes give a representative list of stannanes prepared and the reaction conditions involved.

Further methods which may be employed in the preparation of stannanes of this invention include the following.

(1.) by the action of trimethyltin sodium on aryl halides as described in Chem. Pharm. Bull. 1982, 30, 1731-1737:

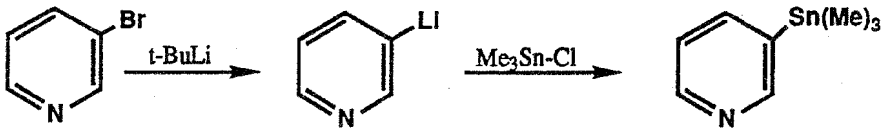


(2.) by heteroatom directed aromatic lithiation process:



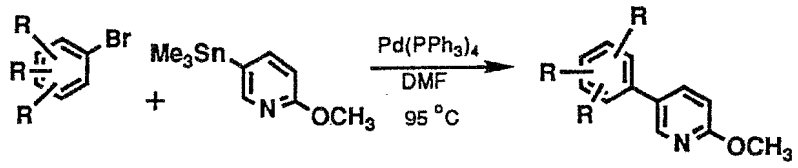
and

(3.) by halogen-lithium exchange:

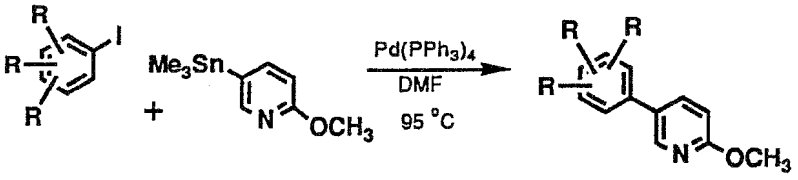


The following are representative coupling reactions which show the preparation of compounds used for the inhibition of cell proliferation

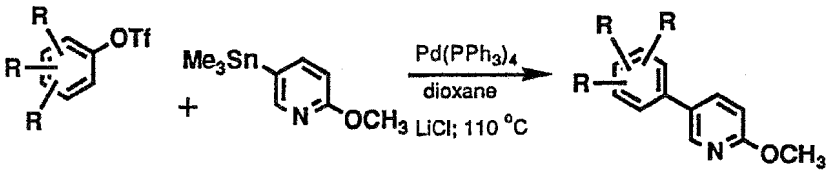
Method A:



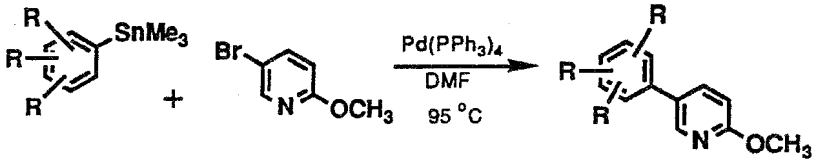
Method B:



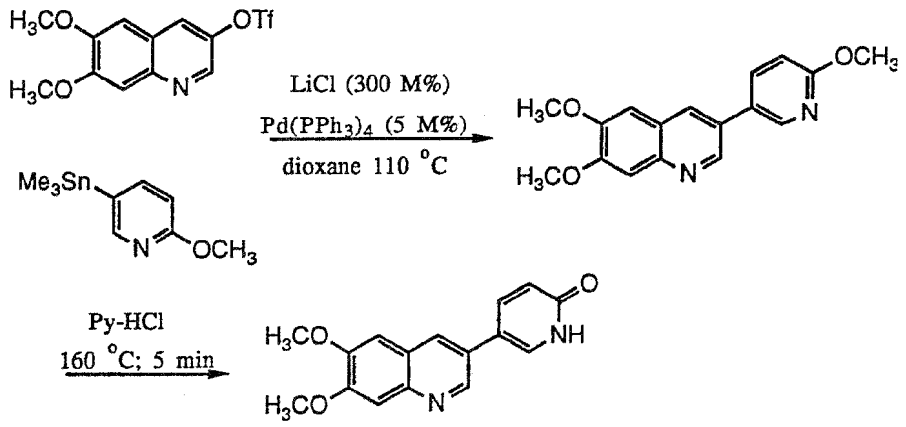
Method C:

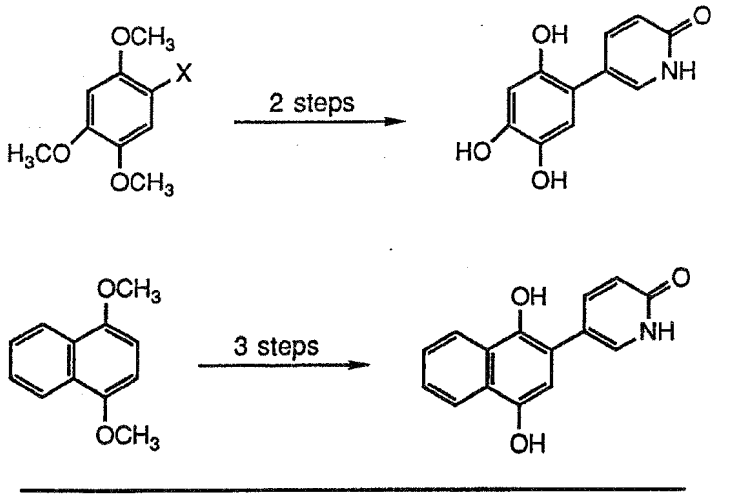


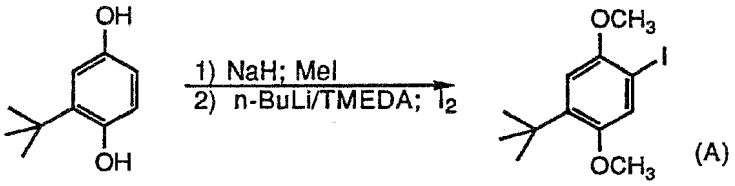
Method D:

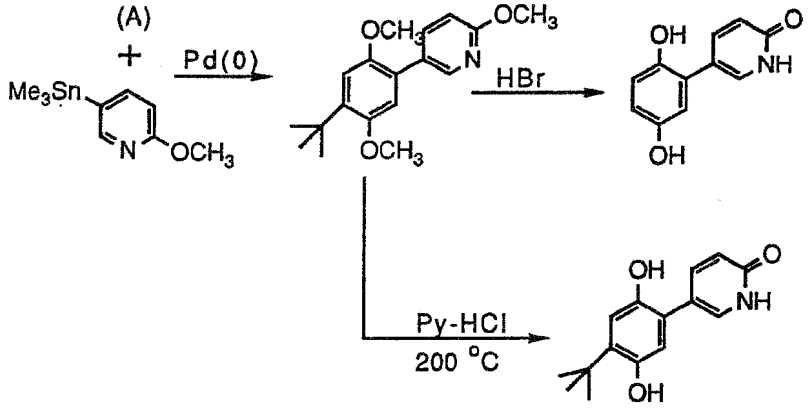


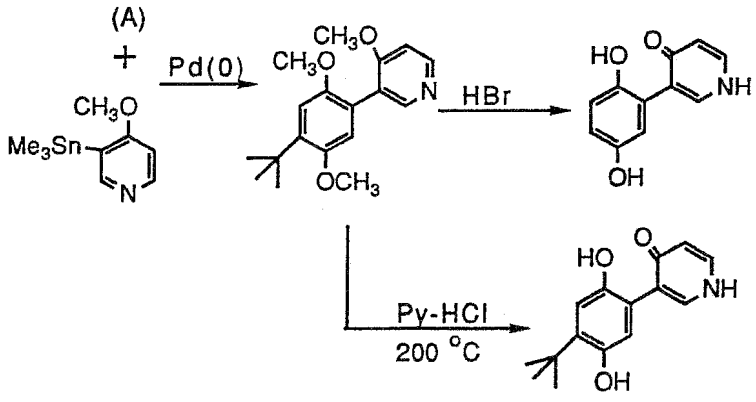
When it is desired that the final product include a 2-(1H) pyridone or 4-(1H) pyridone ring then it is convenient to carry out the condensation on the 2- or 4- alkoxy pyridine followed by selective dealkylation. This can be seen by the following representative scheme.




OCH3
X
H3CO
OCH3
2 steps
OH
NH
O
HO
OH
OCH3
3 steps
OH
NH
O
OH


OH
OH
1) NaH; MeI
2) n-BuLi/TMEDA; I2
OCH3
I
OCH3
(A)


(A)
+
Me3Sn
N
OCH3
Pd(0)
OCH3
OCH3
N
OCH3
HBr
OH
NH
O
OH
Py-HCl
200 °C
OH
NH
O
OH


(A)
+
Me3Sn
CH3O
N
Pd(0)
CH3O
CH3O
N
OCH3
HBr
HO
O
NH
OH
Py-HCl
200 °C
HO
O
NH
OH

The compounds of the present invention may be prepared by the following representative examples.

EXAMPLE 1

2-methoxy-5-trimethylstannylpyridine

A solution of 1.74 g (9.26 mmol) of 2-methoxy-5-bromopyridine, 3.84 mL (6.07 g; 18.5 mmol) of hexamethylditin and 516 mg (0.446 mmol) of Pd $(PPh_3)_4$ in 35 mL of dry toluene is flushed thoroughly with nitrogen and heated to 90°C for 4 hours. The mixture is then evaporated and chromatographed on silica gel (eluting with hexane and then with 95:5 hexane/ethyl acetate) to give 2-methoxy-5-trimethylstannylpyridine as a colorless oil which is used directly in the next step.

EXAMPLE 2

When the procedure of Example 1 is followed and 2-methoxy-5-bromopyridine is replaced by the compounds of Table I below, then the compounds of Table II below are prepared. (Methods outlined on page 14 may also be used.)

TABLE I

2-methoxyphenyl bromide
3-methoxyphenyl bromide
4-methoxyphenyl bromide
2,3-dimethoxyphenyl bromide
2,4-dimethoxyphenyl bromide
2,5-dimethoxyphenyl bromide
2,6-dimethoxyphenyl bromide
3,4-dimethoxyphenyl bromide
3,5-dimethoxyphenyl bromide
3,4,5-trimethoxyphenyl bromide
2,3,4-trimethoxyphenyl bromide
2,5-dimethoxy-4-t-butylphenyl bromide
2,5-dimethoxy-4-phenylphenyl bromide

4-bromopyridazine
1-bromonaphthalene
2-bromonaphthalene
2-bromo-6-methoxynaphthalene
2-bromo-6,7-dimethoxynaphthalene
2-bromoquinoline
3-bromoquinoline
4-bromoquinoline
5-bromoquinoline
6-bromoquinoline
6,7-dimethoxy-3-bromoquinoline
6-methoxy-3-bromoquinoline
7-methoxy-3-bromoquinoline
7,8-dimethoxy-3-bromoquinoline
6,7-dichloro-3-bromoquinoline
4-bromoisoquinoline
3-bromoisoquinoline
1-bromoisoquinoline
6,7-dimethoxy-3-bromoisoquinoline
N-methanesulfonyl-3-bromoindole
N-methanesulfonyl-5-bromoindole
N-methanesulfonyl-3-bromo-5-methoxyindole
N-methanesulfonyl-3-bromo-5-chloroindole
2-bromobenzothiophene
3-bromobenzothiophene
8-bromopurine
7-methyl-2-bromopurine
3-bromopyrido-[3,4-b]-pyridine

TABLE II

2-methoxyphenyl trimethylstannane
3-methoxyphenyl trimethylstannane
4-methoxyphenyl trimethylstannane
2,3-dimethoxyphenyl trimethylstannane
2,4-dimethoxyphenyl trimethylstannane
2,5-dimethoxyphenyl trimethylstannane

3-trimethylstannylfuran
t-butyl 5-trimethylstannyl-2-furoate
2-trimethylstannylthiazole
2-trimethylstannyloxazole
1-methyl-3-trimethylstannylpyrazole
5-trimethylstannylpyrimidine
2-trimethylstannylpyrazine
4-trimethylstannylpyridazine
1-trimethylstannylnaphthalene
2-trimethylstannylnaphthalene
2-trimethylstannyl-6-methoxynaphthalene
2-trimethylstannyl-6,7-dimethoxynaphthalene
2-trimethylstannylquinoline
3-trimethylstannylquinoline
4-trimethylstannylquinoline
5-trimethylstannylquinoline
6-trimethylstannylquinoline
6,7-dimethoxy-3-trimethylstannylquinoline
6-methoxy-3-trimethylstannylquinoline
7-methoxy-3-trimethylstannylquinoline
7,8-dimethoxy-3-trimethylstannylquinoline
6,7-dichloro-3-trimethylstannylquinoline
4-trimethylstannylisoquinoline
3-trimethylstannylisoquinoline
1-trimethylstannylisoquinoline
6,7-dimethoxy-3-trimethylstannylisoquinoline
N-methanesulfonyl-3-trimethylstannylindole
N-methanesulfonyl-5-trimethylstannylindole
N-methanesulfonyl-3-trimethylstannyl-5-methoxyindole
N-methanesulfonyl-3-trimethylstannyl-5-chloroindole
2-trimethylstannylbenzothiophene
3-trimethylstannylbenzothiophene
8-trimethylstannylpurine
7-methyl-2-trimethylstannylpurine
3-trimethylstannylpyrido-[3,4-b]-pyridine

3,5-dichlorophenol
3,5-bis(trifluoromethyl)phenol
3-dimethylaminophenol
o-cresol
m-cresol
p-cresol
α,α,α-trifluoro-p-cresol
3-ethylphenol
4-tert-butylphenol
2,4-dimethylphenol
2,5-dimethylphenol
3,4-dimethylphenol
4-benzyloxyphenol
2-phenylphenol
4-phenylphenol
2,3,5-trimethyphenol
4-nitrophenol
4-acetylaminophenol
2-bromo-4-methylphenol
3'-hydroxyacetophenone
4'-hydroxyacetophenone
methyl 3-hydroxybenzoate
methyl 4-hydroxy-3-methoxybenzoate
N,N-dimethyl-4-hydroxybenzamide
1-naphthol
2-naphthol
6-methoxy-1-naphthol
6-methoxy-2-naphthol
6,7-dimethoxy-1-naphthol
6,7-dimethoxy-2-naphthol
5,8-dimethoxy-2-naphthol
6-bromo-2-naphthol
2-hydroxyquinoline
2-hydroxy-4-methylquinoline
6,7-dimethoxy-2-hydroxyquinoline
3-hydroxyquinoline
4-hydroxyquinoline

2,4-dimethylphenyl trifluoromethane sulfonate
2,5-dimethylphenyl trifluoromethane sulfonate
3,4-dimethylphenyl trifluoromethane sulfonate
4-benzyloxyphenyl trifluoromethane sulfonate
2-phenylphenyl trifluoromethane sulfonate
4-phenylphenyl trifluoromethane sulfonate
2,3,5-trimethyphenyl trifluoromethane sulfonate
4-nitrophenyl trifluoromethane sulfonate
4-acetamidophenyl trifluoromethane sulfonate
2-bromo-4-methylphenyl trifluoromethane sulfonate
3-acetylphenyl trifluoromethane sulfonate
4-acetylphenyl trifluoromethane sulfonate
3-methoxycarbonylphenyl trifluoromethane sulfonate
2-methoxy-4-methoxycarbonylphenyl trifluoromethane sulfonate
4-N,N-dimethylaminocarbonylphenyl trifluoromethane sulfonate
naphth-1-yl trifluoromethane sulfonate
naphth-2-yl trifluoromethane sulfonate
6-methoxynaphth-1-yl trifluoromethane sulfonate
6-methoxynaphth-2-yl trifluoromethane sulfonate
6,7-dimethoxynaphth-1-yl trifluoromethane sulfonate
6,7-dimethoxynaphth-2-yl trifluoromethane sulfonate
5,8-dimethoxynaphth-2-yl trifluoromethane sulfonate
6-bromonaphth-2-yl trifluoromethane sulfonate
quinolin-2-yl trifluoromethane sulfonate
4-methylquinolin-2-yl trifluoromethane sulfonate
6,7-dimethoxyquinolin-2-yl trifluoromethane sulfonate
quinolin-2-yl trifluoromethane sulfonate
quinolin-4-yl trifluoromethane sulfonate
6,7-dimethoxyquinolin-4-yl trifluoromethane sulfonate
7-chloroquinolin-4-yl trifluoromethane sulfonate
isoquinolin-1-yl trifluoromethane sulfonate
isoquinolin-5-yl trifluoromethane sulfonate
pyridin-2-yl trifluoromethane sulfonate
pyridin-3-yl trifluoromethane sulfonate
pyridin-4-yl trifluoromethane sulfonate
2,3-dimethoxypyridin-5-yl trifluoromethane sulfonate
5-chloro-2-pyridin-2-yl trifluoromethane sulfonate

EXAMPLE 7

5-(3,4-dimethoxyphenyl)-2-methoxypyridine

A solution of 2.00 g (6.64 mmol) of 4-trimethylstannylveratrole, 2.49 g (13.2 mmol) of 2-methoxy-5-bromopyridine and 370 mg (0.332 mmol) of Pd $(PPh_3)_4$ in 30 mL of dry dimethylformamide is flushed thoroughly with nitrogen and heated to 90°C for 12 hours. The reaction mixture is partitioned between ethyl acetate (150 mL) and water (100 mL). The aqueous layer is back extracted with ethyl acetate (100 mL) and the combined organics are washed with brine (75 mL), dried ($MgSO_4$) and evaporated to give a crude yellow oil. The oil is chromatographed on silica gel (eluting with 95:5 hexane/ethyl acetate and then with 9:1 hexane/ethyl acetate) which gives 5-(3,4-dimethoxyphenyl)-2-methoxypyridine (m.p 83-84°C.)

EXAMPLE 8

When the procedure of Example 7 is followed and 2-methoxy-5-bromopyridine is replaced with the bromo compounds of Example 2, Table I, then the corresponding products are obtained.

EXAMPLE 9

When the procedure of Example 7 is followed and 4-trimethylstannylveratrole is replaced by the stannanes of Example 2, Table II, then the corresponding products are obtained.

EXAMPLE 10

When the procedure of Example 7 is followed and 2-methoxy-5-bromopyridine is replaced with the bromo compounds of Example 2, Table I and 4-trimethylstannylveratrole is replaced by the stannanes of Example 2, Table II, then the corresponding products are obtained. A representative list of compounds so prepared are shown below in Table VI.

EXAMPLE 12

When the procedure of Example 11 is followed and 2-methoxy-5-trimethylstannylpyridine is replaced by the stannanes of Example 2, Table II, then the corresponding products are obtained.

EXAMPLE 13

When the procedure of Example 11 is followed and 6,7-dimethoxy-quinolin-3-yl trifluoromethane sulfonate is replaced by the triflates of Example 4, Table IV, then the corresponding products are prepared.

EXAMPLE 14

When the procedure of Example 11 is followed and 2-methoxy-5-trimethylstannylpyridine is replaced by the stannanes of Example 2, Table II, and 6,7-dimethoxyquinolin-3-yl trifluoromethane sulfonate is replaced by the triflates of Example 4, Table IV, then the corresponding products are prepared. A representative list of compounds so prepared is shown below in Table VII.

TABLE VII

3-(thien-3-yl)-6,7-dimethoxyquinoline (m.p. 116-118°C)
2-methoxy-5-(3,4,5-trimethoxyphenyl)pyridine (m.p. 71-72°C)
4-(thien-3-yl)-6,7-dimethoxyquinoline (m. p. 134-135°C)
2-(thien-3-yl)-6,7-dimethoxyquinoline (135.5-138°C)
3-(quinolin-3-yl)-6,7-dimethoxyquinoline (m. p. 190.5-191°C)
3-(thien-3-yl)-6,7-dichloroquinoline (m.p. 167-167.5°C)
3-(thien-3-yl)-7-methoxyquinoline (m.p. 122-124°C)
3-(3,4-dichlorophenyl)-6,7-dimethoxyquinoline (m. p.184-186°C)
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline (m. p. 162.5-164.5°C)
3-(naphth-2-yl)-6,7-dimethoxyquinoline (m. p. 162.5-165°C)
3-(4-phenyl)phenyl-6,7-dimethoxyquinoline (m. p. 143-145°C)
3-(thien-2-yl)-6,7-dimethoxyquinoline (m. p. 122.5-124°C)
3-(5-methoxythien-2-yl)-6,7-dimethoxyquinoline (111-113°C)
4-phenyl-6,7-dimethoxyquinoline (m. p. 124-125°C)
3-(5-chlorothien-2-yl)-6,7-dimethoxyquinoline (131.5-132°C)

EXAMPLE 18

5-[(2,5-dihydroxy-4-t-butyl)phenyl]pyridine

When the procedure of Example 17 is followed and 2-methoxy-5-[(2,5-dimethoxy-4-t-butyl)phenyl]pyridine is replaced by 5-[2,5-dimethoxy-4-t-butyl)-phenyl]pyridine, the product obtained is 5-[(2,5-dihydroxy-4-t-butyl)phenyl]-pyridine (m.p. 202-204°C).

EXAMPLE 19

5-(2,5-dihydroxyphenyl)-2(1H)-pyridone

A solution of 502 mg (2.05 mmol) of 2-methoxy-5-(2,5-dimethoxy-phenyl)pyridine in 20 mL of 48% hydrobromic acid (aqueous) is refluxed for 6 hours, cooled to ca. 25°C and diluted with 150 mL of water. The mixture is neutralized with solid $NaHCO_3$, cooled to 0°C and the resulting solid product collected by filtration. The solid is washed well with water, collected by centrifugation, then further purified by recrystalization in methanol to obtain 5-(2,5-dihydroxyphenyl)-2(1H)-pyridone (m.p. 303-306°C dec).

EXAMPLE 20

When the procedure of Example 19 is followed and 2-methoxy-5-(2,5-dimethoxyphenyl)pyridine is replaced by 2-methoxy-5-(3,4-dimethoxy-phenyl)pyridine, 2-methoxy-5-(3,4,5-trimethoxyphenyl)pyridine or 5-(2,5-dimethoxyphenyl)pyridine, then the compounds prepared are 5-(3,4-dihydroxy-phenyl)-2(1H)-pyridone (m.p. 307-310°C); 5-(3,4,5-trihydroxyphenyl)-2(1H)-pyridone (m.p. 300°C) and 5-(2,5-dihydroxyphenyl)pyridine (m.p. 216-218°C).

EXAMPLE 21

When the procedure of Example 17 is followed and 2-methoxy-5-[(2,5-dimethoxy-4-t-butyl)phenyl]pyridine is replaced by 2-methoxy-5-(6,7-dimethoxy-quinolin-3-yl)pyridine and the reaction is carried out at 160°C for 5 minutes, then the product prepared is 5-(6,7-dimethoxyquinolin-3-yl)-2(1H)-pyridone (m.p. 259-261°C).

EXAMPLE 24

When the procedure of Example 23 is followed and 2-amino-4,5-dimethoxybenzaldehyde is replaced with 2-aminobenzaldehyde, then the product prepared is 3-(indol-3-yl)quinoline (m.p. 173-175°C).

EXAMPLE 25

When the procedure of Example 23 is followed and indol-3-yl-acetaldehyde is replaced by phenylacetaldehyde then the product prepared is 3-phenyl-6,7-dimethoxyquinoline (m.p. 126.5-128°C)

EXAMPLE 26

6,7-dimethoxy-4-hydroxy-3-(thien-3-yl)-2(1H)-quinoline

A mixture of (0.632g) 3,4-dimethoxyaniline, (1.00 g) diethyl thien-3-ylmalonate and (20 ml) diphenyl ether are heated at approximately 200°C for 4 hours. The reaction mixture is extracted with 0.IN NaOH solution and the alkaline solution then acidified with IN HCl and cooled in an ice water bath. The precipitate is collected, washed with ether and dried. The solid is then heated in EtOH, filtered and the filtrate evaporated in vacuo to give a light brown solid which is triturated with ether, filtered, and dried to give 6,7-dimethoxy-4-hydroxy-3-(thien-3-yl)-2(1H)-quinoline (m.p. 300°C dec.).

EXAMPLE 27

2-(thien-2-yl)-4-carboxy-6,7-dimethoxyquinoline

To a boiling solution of 2-thiophenecarboxaldehyde (1.22 ml), pyruvic acid (0.904 ml) and 50 ml absolute EtOH is added dropwise a solution of 3,4-dimethoxyaniline (2.00 g) in 100 ml EtOH. The mixture is refluxed for approximately 4 hours, then stored at room temperature overnight. The greenish-yellow precipitate is collected by filtration, washed with fresh EtOH then with ether and allowed to air dry to obtain 2-(thien-2-yl)-4-carboxy-6,7-dimethoxyquinoline (m.p. 260°-263°C).

Step A 3-cyclohexylethynyl-6,7-dimethoxyquinoline

This reaction is carried out under anhydrous conditions. Cyclohexylacetylene (700 mg; 6.47 mmol) in 10 mL. THF is cooled to O°C. To this is added 2.5 M n-BuLi (3.0 mL; 7.44 mmol) and stirred for 30 min. at O°C under N_2 atm and then 1.0 M $ZnCl_2$ (7.4 mL; 7.44 mmol). This is allowed to warm to room temperature and stirred for 3/4 hour. The reaction mixture is transferred via cannula to a flask containing 6,7-dimethoxyquinolin-3-yl trifluoromethane sulfonate (500 mg; 1.48 mmol) and $Pd(PPh_3)_4$ (83 mg; 0.074 mmol) in 4 mL of THF. This is then heated to 50°C under N_2 for 4 1/2 hours. The reaction mixture is then poured into 90 mL of 10% NH_4OH, diluted with $CHCl_3$ and stirred for 20 min. The aqueous layer is separated, and the organic layer washed with brine, dried over $MgSO_4$, filtered, evaporated and chromatographed with 4:1 hexane : EtOAc to obtain 3-cyclohexylethynyl-6,7-dimethoxyquinoline, which is recrystallized from hexane, identified by NMR and used directly in the next step.

Step B 3-cyclohexylethyl-6,7-dimethoxyquinoline

To 3-cyclohexylethynyl-6,7-dimethoxyquinoline (215 mg; 0.73 mmol) in 10mL CH_3OH and 20 mL glacial acetic acid is added 22 mg 10% Pd/C. H_2 is bubbled through the reaction mixture and then filtered, evaporated to dryness and diluted with distilled water. This is then neutralized with Na_2CO_3, extracted with EtOAc, washed with brine, dried ($MgSO_4$), evaporated to dryness and chromatographed with 8:2/hexane: EtOAc to obtain 3-cyclohexylethyl-6,7-dimethoxyquinoline.

Calc'd: C: 76.22; H: 8.47; N: 4.69

Found: C: 75.08; H: 8.32; N: 4.59

EXAMPLE 32

3-benzyloxy-6,7-dimethoxyquinoline

To 3-hydroxy-6,7-dimethoxyquinoline (150 mg; 0.73 mmol) in 3 mL THF is added benzyl bromide (0.13 mL;188 mg; 1.10 mmol) and NaH (59mg; 1.46 mmol). This is stirred at room temperature for 1 hour and 25 mg of NaH added followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone

4-(thien-3-yl)isoquinoline hydrochloride (m.p. 179-183°C)
4-(4-methoxyphenyl)isoquinoline hydrochloride (m.p. 196-199°C)
6,7-dimethyl-2-(thien-3-yl)-quinoxaline (m.p. 142-143.5°C)
4-(thien-3-yl)-6,7-dimethoxyquinazoline (m.p. 148.5-151.5°C)
4-benzyl-6,7-dimethoxyquinazoline (m.p. 122.5-125°C)
2-phenyl-6,7-diethoxyquinoxaline hydrochloride (m.p. 180-185°C)
2-(3-thienyl)-6,7-diethoxyquinoxaline hydrochloride (m.p. 217-224°C)
2-(5-chloro-2-thienyl)-6,7-diethoxyquinoxaline hydrochloride (m.p. 189-194°C)
2-(5-chloro-2-thienyl)-6,7-dimethoxyquinoxaline hydrochloride (m.p. 218-25°C)
3-(3-fluoro-4-methoxyphenyl)-7-fluoroquinoline (m.p. 138-140.5°C)
2-chloro-3-(thien-3-yl)-6,7-dimethoxyquinoline (m.p. 138.5-139.5°C)
2-methyl-3-(thien-3-yl)-6,7-dimethoxyquinoline (m.p. 132-132.5°C)
3-(thien-3-yl)-5-fluoroquinoline (m.p. 87.5-89°C)
2-(4-methylphenyl)-3-methyl-4(3H)quinazolinone (m.p. 139-141°C)
ethyl 4-(6,7-dimethoxyquinolin-3-yl)benzoate (m.p. 165-166°C)
4-phenylpropyl-6,7-dimethoxyquinoline hydrochloride (m.p. 144-147°C)
3-(thien-3-yl)-5,7-dimethylquinoline (m.p. 109.5-111°C)
3-(5-chlorothien-2-yl)-6,7-dimethylquinoline (m.p. 131.5-132.5°C)
3-(3-fluoro-4-methoxyphenyl)-7-methoxy-4(1H)-quinolone (m.p. 291-293°C)
3-(3-fluoro-4-methoxyphenyl)-5,7-dimethylquinoline (m.p. 109-110°C)
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline-4-N-oxide (m.p. 224-226°C)
2-phenyl-6,7-dimethoxyquinoxaline-4-N-oxide (m.p. 219-222°C)
2-(4-methoxyphenyl)quinazolin-4(3H)-one (m.p. 244-247°C)
3-(thien-3-yl)-6,7-difluoroquinoline (m.p. 141.5-143.5°C)
3-(4-methoxyphyenyl)-7-methoxy-1-naphthalenol (m.p. 155-159°C)
2-phenyl-6,7-dimethoxy-4H-3,1-benzoxazin-4-one (m.p. 198-201°C)
2-(4-methoxyphenyl)-6,7-dimethoxyquinazolin-4(3H)-one (m.p. 288-291°C)
methyl 3-[3-(3-fluorophenyl)quinoline-6-yl]propenoate (m.p.184-186°C)
ethyl 4-[3-(3-fluorophenyl)quinolin-6-yl]benzoate (m.p. 168-170°C)
3-benzyloxy-6,7-dimethoxyquinoline (m.p. 146.5-148.5°C)
3-(2-methoxypyrid-5-yl)-6,7-dimethoxyquinoline (m.p. 170.5-171.5°C)
3-cyclohexylethyl-6,7-dimethoxyquinoline (oil) (Calc'd / Fnd; C: 76.22 /75.10; H: 8.42 / 8.30; N: 4.68 / 4.60)

gel is dried and autoradiographed as described above. The relevant radioactive bands are cut and counted in the Cerenkov mode. The K_m for ATP determined in this fashion is found to be 7.2 μM. With use of the 10-sec assay protocol, the EGF concentration dependence of EGF-RK autophosphorylation is determined.

Inhibition of EGF-R Autophosphorylation

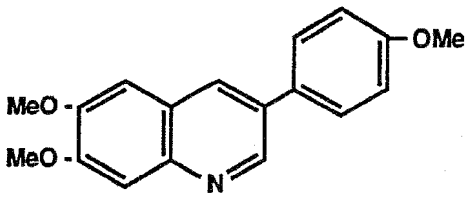
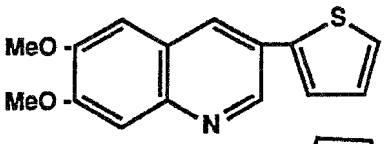
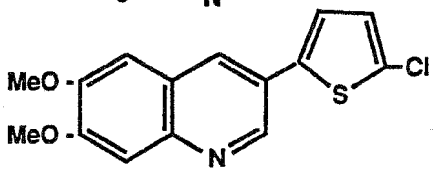
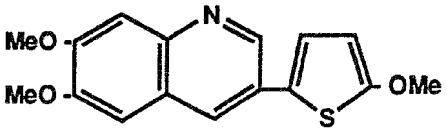
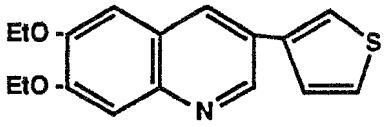
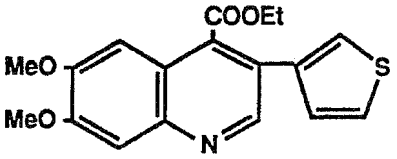
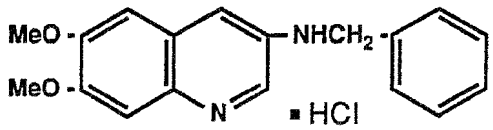
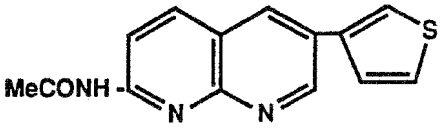
A431 cells were grown to confluence on human fibronectin coated tissue culture dishes. After washing 2 times with ice-cold PBS, cells were lysed by the addition of 500 μl/ dish of lysis buffer (50 mmol Hepes, pH 7.5, 150 mmol NaCl, 1.5 mmol $MgCl_2$, 1 mmol EGTA, 10% glycerol, 1% triton X-100, 1 mmol PMSF, 1 mg/ml aprotinin, 1 mg/ml leupeptin) and incubating 5 minutes at 4°C. After EGF stimulation (500 μg/ml 10 minutes at 37°C) immunoprecipitation was performed with anti EGF-R (Ab 108) and the autophosphorylation reaction (50 μl aliquots, 3 μCi [γ-^{32}P]ATP) sample was carried out in the presence of 2 or 10 μM of compound of the present invention, for 2 minutes at 4°C. The reaction was stopped by adding hot electrophoresis sample buffer. SDA-PAGE analysis (7.5% els) was followed by autoradiography and the reaction was quantitated by densitometry scanning of the x-ray films.

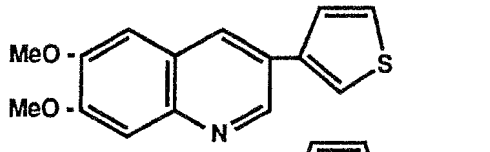
In order to test the present compounds for selective inhibition, the procedure is repeated using PDGF stimulation in place of EGF stimulation. "IC_{50}," as used below refers to the concentration of inhibitor (μM) at which the rate of autophosphorylation is halved, compared with media containing no inhibitor.

Inhibition of PDGF-R Autophosphorylation

Lysate from NIH 3T3 cells was diluted one-third in Triton-free buffer and stimulated with 10 ng/ml PDGF for 30 minutes at 4°C. The equivalent of 1/15 of a 175-cm^2 plate of lysate was used per sample. The stimulated lysate was then immunoprecipitated with rabbit polyclonal anti-PDGF-receptor antibodies raised against a synthetic peptide from the COOH-terminal region (amino acids 1094-1106) or the human PDGF-receptor ß-subunit and added to increasing concentrations of test compound of the present invention. After 10 minutes at 4°C, 10 μCi of [γ-^{32}P]ATP were added and further incubated for 10 minutes at 4°C. Samples were separated by SDS-PAGE on 6% gels.

Inhibition of Cell Proliferation as
Measured by Inhibition of DNA Synthesis

COMPOUND	Inhibition of PDGF-R cell-free Autophosphorylation IC_{50} (μM)
	0.003-0.015
	0.050-0.10
	0.007
	0.2-1
	0.06-0.08
	1.0-2.0
	0.02-0.08
	0.05-0.1



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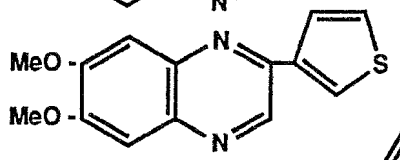

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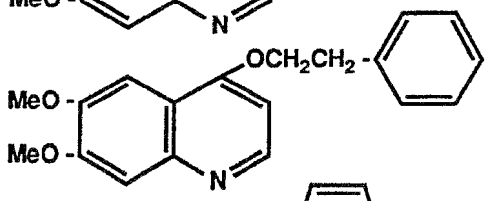

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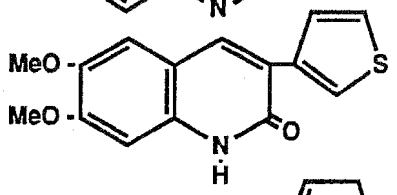

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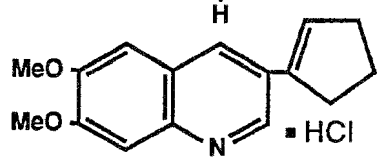

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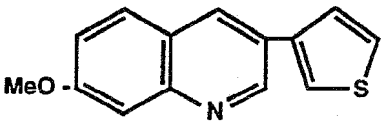

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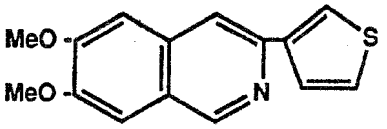
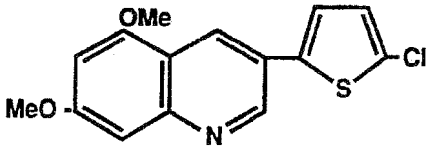


7-12



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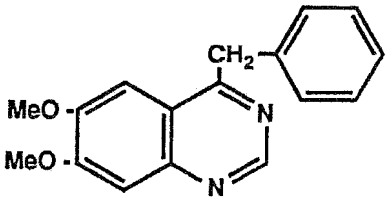


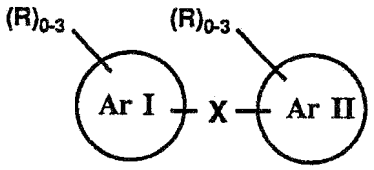
15-20

WE CLAIM:

1. A method of inhibiting abnormal cell proliferation in a patient suffering from a disorder characterized by such proliferation comprising the administration thereto of an EGF and/or PDGF receptor inhibiting effective amount of a compound having a bis ring system wherein the first ring is aryl or heteroaryl and the second ring is aryl, heteroaryl, carbocyclic or heterocarbocyclic and wherein said rings comprise either a substituted or unsubstituted monocyclic ring containing 0 to about 2 hetero atoms, or a bicyclic ring containing 0 to about 4 hetero atoms, or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition for inhibiting abnormal cell proliferation comprising, in admixture with a pharmaceutically acceptable carrier, a pharmaceutically effective amount of a compound according to claim 1.

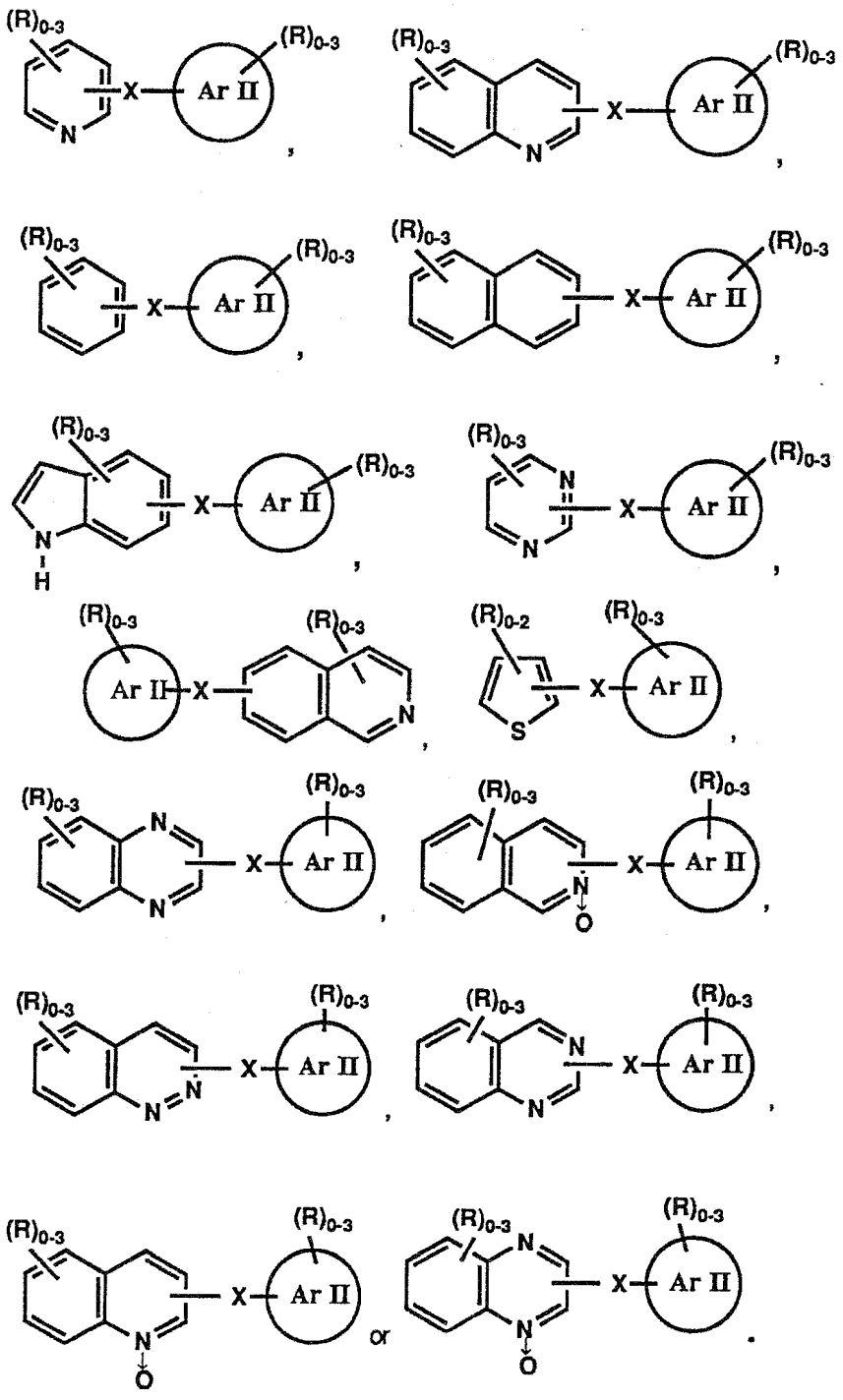
3. A method according to claim 1 comprising administering to said patient a pharmaceutically effective amount of a pharmaceutical composition containing, in admixture with a pharmaceutically acceptable carrier, a compound, or a pharmaceutically acceptable salt thereof, of the formula:



wherein

Ar I is a substituted or unsubstituted mono- or bicyclic aryl or heteroaryl ring system of about 5 to about 12 atoms and where each monocyclic ring may contain 0 to about 3 hetero atoms, and each bicyclic ring may contain 0 to about 4 hetero atoms selected from N, O and S provided said hetero atoms are not vicinal oxygen and/or sulfur atoms and where the substituents may be located at any appropriate position of the ring system and are described by R.;

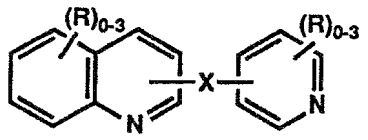
Ar II may be as described for **Ar I** or it may also be saturated carbocyclic wherein said ring comprises either a substituted or unsubstituted



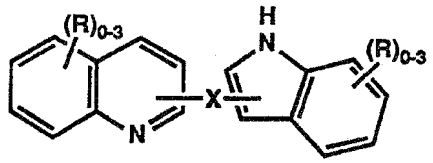
5

7. A method according to claim 6 where said compound is of the formula

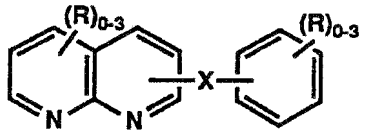
12. A method according to claim 6 where said compound is of the formula



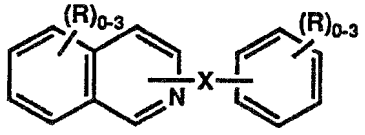
13. A method according to claim 6 where said compound is of the formula



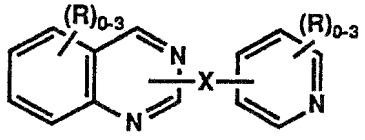
14. A method according to claim 6 where said compound is of the formula

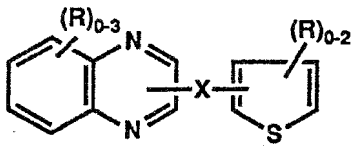


15. A method according to claim 6 where said compound is of the formula

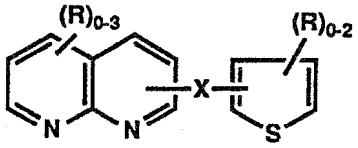


16. A method according to claim 6 where said compound is of the formula

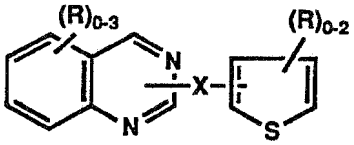




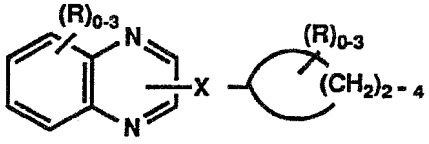
23. A method according to claim 6 where said compound is of the formula



24. A method according to claim 6 where said compound is of the formula



25. A method according to claim 6 where said compound is of the formula



26. A method according to claim 1 where said compound administered is selected from the group consisting of

3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-7-methoxyquinoline;
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(2-chlorothien-2-yl)-6,7-dimethoxyquinoline;
3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;

27. A method for the treatment of psoriasis in a patient suffering from such disorder comprising administering to said patient an effective anti-psoriatic composition according to claim 2.

28. A method for the treatment of atherosclerosis in a patient suffering from such disorder comprising administering to said patient an effective anti-atherosclerotic composition according to claim 2.

29. A method for the treatment of vascular reocclusion in a patient suffering from such disorder comprising administering to said patient an effective amount of a composition according to claim 2.

30. A method according to claim 29 where said disorder results from an angioplastic procedure.

31. A compound selected from the group consisting of:
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-7-methoxyquinoline;
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(2-chlorothien-2-yl)-6,7-dimethoxyquinoline;
3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
3-(2-chlorothien-2-yl)-5,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethylquinoline;
3-(1-cyclopent-1-enyl)-6,7-dimethoxyquinoline;
3-cyclopentyl-6,7-dimethoxyquinoline;
4-(3-phenylpropyloxy)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline-N-oxide;
3-(2-chlorothiophen-5-yl)-5,7-dimethoxyquinoline;
3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(3-fluorophenyl)-6,7-dimethoxyquinoline;
4-(2-phenylethoxy)-6,7-dimethoxyquinoline;
3-(4-methoxybenzyloxy)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
2-(thien-3-yl)-6,7-dimethoxyquinoxaline;
2-phenyl-6,7-dimethoxyquinoxaline;